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Does Follicularity in Large Cell Lymphoma Predict Outcome after Autologous Stem Cell Transplantation?

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ABSTRACT

The purpose of this study was to evaluate whether follicular histology in large cell lymphoma influences treatment outcomes after autologous stem cell transplantation (ASCT). It remains an area of controversy whether the natural history of follicular large cell lymphoma (FLCL) is akin to diffuse large cell lymphoma (DLCL) with curative potential or is more similar to indolent follicular lymphomas with a pattern of late relapses after intensive chemotherapy. Although ASCT is a potentially curative treatment for patients with recurrent DLCL, the effectiveness of this approach in patients with FLCL is unclear. We undertook a retrospective analysis of 332 patients with large cell lymphoma who underwent ASCT at the City of Hope Comprehensive Cancer Center. With a median follow-up of 31 months, the projected 10-year overall survival and disease-free survival were similar between patients with FLCL and DLCL. Analysis of prognostic factors demonstrated that although age, chemotherapy refractoriness, and disease status at the time of ASCT were predictive of overall survival/disease-free survival, follicularity did not influence the outcome. Furthermore, the similar plateau in the survival curve for the DLCL and FLCL patients suggests that the behavior of FLCL is similar to that of DLCL and that FLCL is potentially curable with ASCT.

KEY WORDS

Follicular large cell lymphoma • Transplantation

INTRODUCTION

Over the past 20 years, several classification schemes have been developed for non-Hodgkin lymphoma (NHL) that are based on the observation that the clinical behavior of various follicular lymphomas can be highly variable and on the need for a more precise and reproducible system to guide clinicians. At present, the curative potential of follicular large cell lymphoma (FLCL), otherwise known as follicular grade 3 NHL in the Revised European-American classification (REAL) schema, remains an area of controversy [1]. Some series suggest that FLCL behaves as an indolent lymphoma characterized by late relapses after chemotherapy [2]. Other investigators have demonstrated high complete remission rates and plateaus in disease-free survival (DFS) when these patients were treated with an anthracycline-based regimen [3-5].

The role of autologous stem cell transplantation (ASCT) for this histologic subtype is also unclear. For patients with relapsed NHL, a prospective randomized study has demonstrated that high-dose chemotherapy/radiotherapy with ASCT is superior to conventional salvage therapy [6]. However, the number of patients with FLCL included in the study was small; hence, this question remain unanswered: is ASCT curative, or are there continued late relapses, as occur with other follicular histologic categories [7]? Several retrospective series have addressed this question, but with conflicting results [8,9]. In the Nebraska series, patients with good-prognosis FLCL had an improved survival compared with a similar group of patients

with diffuse large cell lymphoma (DLCL) [8]. In contrast, the series from Princess Margaret Hospital found no prognostic significance to FLCL versus DLCL histological findings [9]. Because of these conflicting results, we evaluated this question in a larger series of patients with sufficient long-term follow-up to capture late relapses.

MATERIALS AND METHODS

This was a retrospective study of 332 patients with large cell NHL who underwent ASCT at the City of Hope Comprehensive Cancer Center between December 1987 and November 2002. Fifty-five patients had FLCL, and 277 had DLCL. All biopsy specimens were reviewed at the City of Hope by an expert hematopathologist, and the most recent biopsy sample before ASCT was classified according to the REAL schema. All FLCL patients had either a core biopsy or excisional biopsy for diagnosis, and 14 of these patients underwent another biopsy at time of relapse before transplantation. Patients with T-cell lymphomas were excluded from analysis. Informed consent was obtained from patients, in compliance with institutional standards. Patients were considered eligible for transplantation if they had not achieved an initial complete remission or if they relapsed after attaining a complete remission with standard-dose chemotherapy. In addition, patients in first complete remission who had high-risk features, as defined by the International Prognostic Index (IPI), were also eligible for transplantation [10].

The median age at transplantation was 52 years (range, 27-63 years) and 46 years (range, 12-75 years) for the FLCL group and the DLCL group, respectively ($P = .005$). Other patient and disease characteristics are summarized in Table 1. A higher proportion of patients in the FLCL group had relapsed disease at the time of ASCT. However, both groups had comparable numbers with a chemotherapy-sensitive relapse. Sensitive relapse was defined as at least a 50% reduction in bidimensional measurements of the size of the tumor with the use of conventional salvage therapy. Patients were considered to be in partial remission if they had a >50% reduction in the diameter of all measurable lesions for at least 3 months and resolution of disease-related symptoms. Patients who had <50% reduction, reappearance of disease-related symptoms, or measurable growth of disease during therapy or within 2 months of completion of treatment were considered to have induction failure. There were more patients with bulky disease in the DLCL group, and there was more bone marrow involvement in the FLCL group. The IPI score was known in 143 patients. The median score was 2 in the FLCL group and 3 in the DLCL group. Cytogenetic information was available for 39 of the FLCL patients. Four of these patients had the 14,18 translocation: 2 in bone marrow and 2 in lymph nodes.

Transplantation screening criteria included normal cardiac function (defined as an ejection fraction >50% by either echocardiogram or multiple gated acquisition scan), adequate pulmonary function (diffusion capacity >50% or forced expiratory volume in 1 second >75% of predicted), and adequate renal function (24-hour creatinine clearance >60 mL/min). Patients were screened for hepatitis A, B, and C virus, though this was not an exclusion criterion. They were required to have no bone marrow involvement with lymphoma on their pretransplantation marrow except for patients with discordant lymphoma, who had <5% residual marrow involvement. There was no upper age limit on transplantation.

Bone marrow and/or peripheral blood progenitor cells (PBPCs) were collected. Methods for marrow and PBPC collection have been previously described [11]. No purging was performed of either marrow or PBPCs. Patients with prior bone marrow involvement at diagnosis received PBPCs. Before 1989, patients received a combination of bone marrow and PBPC. Starting in 1991, all patients received PBPCs preferentially.

Patients were treated with 1 of 3 transplant conditioning regimens. The choice of regimen was based on their prior chemotherapy sensitivity, age, and radiation history. The radiation-based regimen consisted of total body irradiation 1200 cGy delivered in split fractions, followed by etoposide 60 mg/kg (adjusted body weight) and cyclophosphamide 100 mg/kg (ideal body

Table 1. *Patient Characteristics*

Variable	FLCL (n = 55)	DLCL (n = 277)	*P* Value
Median age, y (range)	52 (27-63)	46 (12-75)	.005
Disease status	1 CR/1 PR: 11 (20%)	1 CR/PR: 112 (41%)	<.001
	IF 3 (6%)	IF 61 (22%)	
	REL 40 (74%)	REL 101 (37%)	
		Unk 4 (1%)	
Chemosensitive REL	16 (40%)	42 (70%)	.13
Bone marrow involvement at diagnosis	13 (23%)	35 (13%)	.03
FTBI conditioning	25 (66%)	146 (67%)	.92
Bulky disease >10 cm	9 (19%)	92 (39%)	.009

CR indicates complete remission; PR, partial remission; REL, relapse; Unk, unknown; FTBI, fractionated total body irradiation.

weight). The chemotherapy regimen was either (1) cyclophosphamide 100 mg/kg (ideal body weight), carmustine 150 mg/m^2 × 3, and etoposide 60 mg/kg (adjusted body weight) or (2) carmustine 150 mg/m^2 × 2, etoposide 200 mg/m^2 × 8, cytarabine 200 mg/m^2 × 8, and melphalan 140 mg/m^2 × 1.

Autologous marrow or PBPCs were transported to the bedside in the vapor phase of liquid nitrogen, thawed at bedside in a water bath, and reinfused according to standard institutional guidelines on day 0. Granulocyte colony-stimulating factor was started on day +1 at a dose of 5 μg/kg (until 1999, when as standard practice it was started on day +5 at the same dose) and continued until patients reached an absolute neutrophil count >500 μl for 3 consecutive days.

Supportive care with prophylactic antimicrobials, antifungals, and low-dose heparin for veno-occlusive disease prophylaxis was administered according to institutional guidelines [11]. The only major change in supportive care during the time period covered in the study was a change from vancomycin/neomycin to levofloxacin in 1996 to minimize risks of vancomycin-resistant enterococcus.

Pathology Review

All pathology specimens from diagnosis and the most recent pretransplantation biopsy sample were reviewed at the City of Hope and classified according to the REAL classification. Subclassification of the follicular lymphomas was performed according to the Mann and Berard criteria, which require that >15 cells per high-power field (0.159 mm^2) be large noncleaved cells [12]. T-cell phenotypes were excluded on the basis of immunohistochemistry.

Disease Response Evaluation

Patients had a pretransplantation staging evaluation within 28 days of enrollment onto a transplantation protocol that consisted of computed tomographic scans, bone marrow biopsy, and clinical documentation of disease. The Ann Arbor staging system was used. Posttransplantation disease evaluation was performed with computed tomographic scans at approximately 1 to 2 months after transplantation and then every 6 months for the first 2 years. Subsequently scans were performed yearly for 5 years after ASCT and sooner if clinically indicated. Disease status was assessed according to conventional criteria, as previously described [11].

Statistical Methods

Demographic and disease characteristics were summarized for all patients by using simple descriptive statistics. Two-sided 2-sample *t* tests were used for comparing means between the 2 histologic groups. Survival estimates were calculated according to the product-limit method, and 95% confidence intervals were calculated by using the logit transformation with Greenwood's variance estimate [13]. Factors possibly associated with overall survival (OS), DFS, and relapse were examined by univariate and multivariate Cox regression analysis [14]. The assumption of proportionality of the hazard ratio was tested for each variable. The variables tested included age at transplantation, sex, bulky disease at diagnosis, stage at diagnosis, "B" symptoms, marrow involvement, increased lactate dehydrogenase, and extranodal disease, each at diagnosis and relapse; number of prior chemotherapy regimens; prior radiation therapy; IPI score; disease status; chemosensitivity; and conditioning regimen. The hazard ratio was calculated for each variable, along with the 95% confidence intervals. Multivariate analyses were performed by using a stepwise model selection and model prediction with a threshold $P = .20$ for variable entry and $P = .05$ for retention.

OS was defined as the time from transplantation until death or last contact. Time to relapse was defined as the time from transplantation until confirmed relapse or last contact. DFS was defined as the time from transplantation until relapse or death if the patient did not relapse or until last contact if the patient did not die or relapse.

RESULTS

The median follow-up was 31 months for all surviving patients (range, 0.7-175 months). The median follow-up in the FLCL group was 19 months (range, 1-146 months) and was 34 months (range, 0.7-175 months) for DLCL patients. The projected 10-year OS is 48% (95% CI, 38%-58%) for all patients, 58% (95% CI, 38%-74%) for FLCL, and 46% (95% CI, 34%-57%) for DLCL ($P = .27$; Figure 1). The projected 10-year DFS is 36% (95% CI, 27%-46%) for all patients, 27% (95% CI, 10%-48%) for FLCL, and 38% (95% CI, 28%-49%) for DLCL ($P = .70$; Figure 2). Causes of death were as follows: lymphoma recurrence (77%), transplant-related mortality (19%), and secondary malignancies (4%).

Univariate analysis of the combined group demonstrated that the IPI score, bulky disease at diagnosis, age, disease status at ASCT, and type of conditioning regimen (fractionated total body irradiation versus chemotherapy alone) were predictive of both OS and DFS. However, histological type, ie, follicular versus diffuse, was not predictive of either OS or DFS. Multivariate analysis of the combined group resulted in 1 viable model, which showed chemorefractoriness (relative risk (RR), 3.28; 95% CI, 2.18-4.93) and age (RR, 1.02; 95% CI, 1.01-1.05) as predictive of DFS ($P < .0001$ and $P = .003$, respectively).

In subgroup analysis of patients who underwent

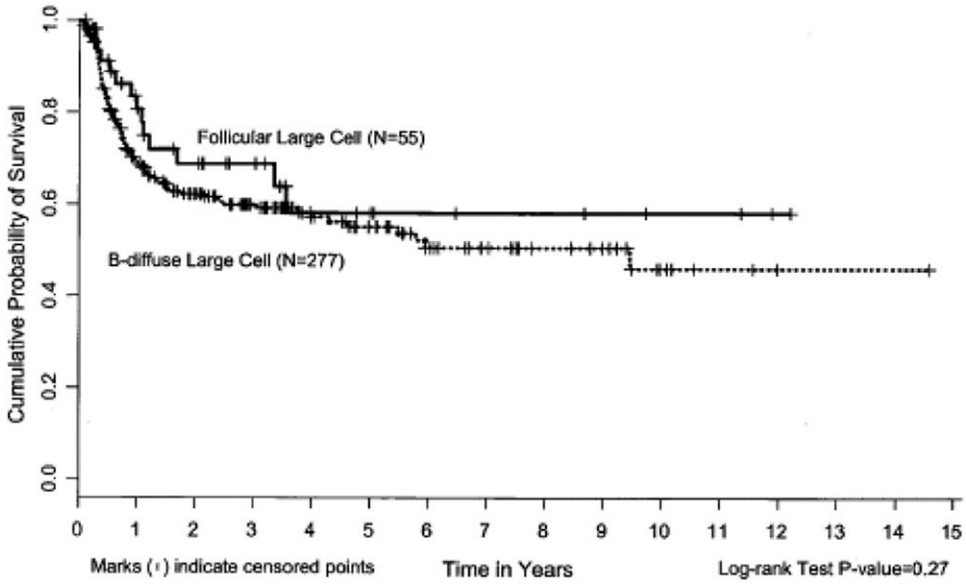

Figure 1. Follicular large cell versus diffuse large cell lymphoma: overall survival (n = 332).

transplantation in sensitive relapse, the 1-year OS was 64% (95% CI, 49%-75%) for all patients, 66% (95% CI, 37%-85%) for FLCL, and 62% (95% CI, 46%-76%) for DLCL patients (P = .33). The 1-year DFS was 53% (95% CI, 39%-65%) for all patients, 62% (95% CI, 35%-81%) for FLCL, and 50% (95% CI, 34%-64%) for DLCL (P = .92).

Subgroup analysis of the first complete remission/partial remission patients was also performed. The 1-year OS was 86% (95% CI, 78%-91%) for all patients, 91% (95% CI, 51%-99%) for FLCL patients, and 86% (95% CI, 77%-91%) for DLCL patients (P = .76). The 1-year DFS was 78% (95% CI, 69%-85%) for all patients, 73% (95% CI, 37%-90%) for FLCL, and 79% (95% CI, 70%-86%) for DLCL (P = .18).

When the groups were analyzed separately by multivariate analysis, bone marrow involvement and the number of prior chemotherapy regimens were significant predictors of OS/DFS in the FLCL group. In the DLCL group, bone marrow involvement at relapse, the IPI score before ASCT, age >30 years at ASCT, and induction failure before ASCT were predictive of OS/DFS. Factors that were associated but did not reach statistical significance included bulky disease at diagnosis and extranodal disease at diagnosis.

DISCUSSION

FLCL is an uncommon malignancy that represents between 3% and 7% of all NHLs [15]. None-

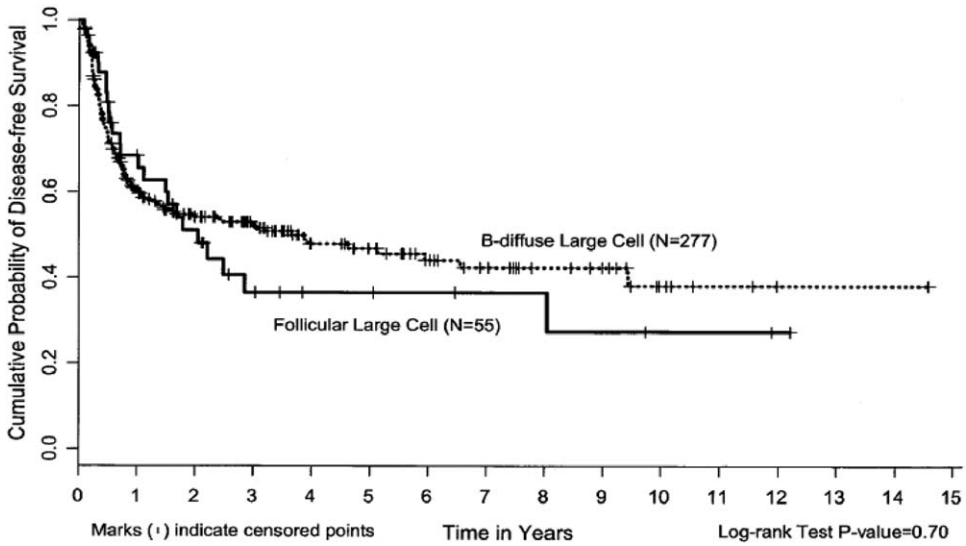

Figure 2. Follicular large cell versus diffuse large cell lymphoma: disease-free survival (n = 332).

theless, it remains a controversial disease in terms of diagnosis, treatment, and prognosis. For example, in the Working Formulation, FLCL is classified as an intermediate-grade lymphoma, whereas in the REAL classification it is designated as follicular center lymphoma grade 3 [1]. Other studies have further attempted to define prognosis by evaluating the clinical significance of the subdivision of follicular grade 3 into 3a and 3b [16,17]. Cytogenetic studies have demonstrated that there is a high frequency of t(14,18) in follicular 3a (73%) but a relatively low frequency in follicular 3b (13%). Although the presence or absence of this translocation does not have prognostic significance for DFS, it does demonstrate the heterogeneity of the follicular lymphomas and may partially explain inconsistencies in the clinical behavior of FLCL [17].

For example, do these lymphomas behave clinically like DLCL, or do they have a pattern of late relapses that resemble indolent lymphomas? Several retrospective studies have attempted to answer this basic question and have tried to define the optimal chemotherapy regimen. Initial series demonstrated the superiority of anthracycline-containing regimens for FLCL similar to DLCL. In a report of 96 patients treated at Stanford University, approximately half the patients received a doxorubicin-containing regimen. The 10-year OS was 65% in this group, versus 42% in the group treated with nonanthracyline regimens [18]. Other studies have confirmed that long-term outcome is similar for DLCL and FLCL patients treated with doxorubicin-based regimens. A series of 100 patients from M.D. Anderson Cancer Center, all treated with a cyclosphosphamide, adriamycin, vincristine, prednisone (CHOP)-bleomycin–based regimen, reported a 72% OS at 5 years with a trend toward a plateau in failure-free survival. The IPI score was predictive of prognosis in this group. Long-term follow-up of a subgroup treated from 1973 to 1981 showed an OS of 21% at 15 years [3]. This outcome is similar to that of DLCL patients treated with CHOP-bleomycin at the same institution [19]. A French series of patients treated with a combination chemotherapy regimen on the LNH87 trial included 89 patients with FLCL. When they were compared with DLCL patients in the trial, there was no significant difference in 5-year OS and DFS [20].

In contrast to the aforementioned studies, other investigators have suggested that there is no plateau in DFS and that there is a continuous pattern of relapse, and this would be more akin to the behavior of indolent lymphomas. For example, the Nebraska study group reported on stage I and II follicular lymphoma patients. Seventy-five percent of these patients had FLCL. The investigators did not see a plateau in OS or event-free survival in this group [21]. Similarly, a South West Oncology Group study of 389 patients, which included 53 patients (14%) with FLCL, showed a continuous decline in the OS curve and a 10-year estimated OS of 37% for the FLCL subgroup. However, this group did not include stage I and II patients and also did not report the number of patients who died of non–lymphoma-related causes [2].

The role of ASCT for FLCL also remains undefined. Dose-intensive chemotherapy/radiotherapy with ASCT has become accepted salvage therapy for patients with relapsed DLCL. The superiority of this approach over conventional-dose chemotherapy for relapsed disease has been confirmed in randomized trials [6]. In addition, prognostic factors for DLCL after ASCT have been identified. These factors include IPI at the time of relapse, bulky disease, and chemosensitivity [22-24]. The use of ASCT for indolent lymphomas has also been extensively studied. Factors influencing ASCT outcome for these patients include chemosensitivity, tumor burden, the number of prior chemotherapy regimens, and BCL-2 status after ASCT [7,25]. These trials also demonstrate that in contrast to DLCL, there is no plateau in the DFS for patients with indolent follicular lymphomas after ASCT. Some of these trials may have included FLCL patients. However, because of the small numbers of patients and the use of various classification systems, it is difficult to extrapolate data for this subgroup. Several retrospective studies have looked specifically at FLCL patients and attempted to identify prognostic factors for outcome after ASCT. The series from Nebraska evaluated 289 patients with large cell lymphoma, 62 of whom had FLCL. The median follow-up was 24 months (range, 3-131 months). They found that tumor bulk, the number of prior chemotherapy regimens, and increased lactate dehydrogenase were significantly predictive for worse failure-free survival [8]. In contrast, follicular histological results had a positive effect on failure-free survival.

The investigators then went on to divide patients into a good-prognosis group (normal lactate dehydrogenase, <3 prior chemotherapy regimens, and nonbulky disease). In this group, on multivariate analysis, follicular histology was an independent predictor of improved OS. In the other patients—ie, the poor-prognosis group—follicularity had no significant effect on outcome. Data from investigators at Princess Margaret Hospital support the latter findings [9]. They performed a retrospective analysis on 36 patients with FLCL and compared them with 90 DLCL patients undergoing ASCT at the same time period. The patient characteristics were relatively evenly matched in both groups except for more bone marrow involvement in the FLCL group. Multivariate analysis indicated that the lymphoma subtype did not influence OS or DFS. There initially seemed to be a survival advantage in the FLCL patients, but at 7 years the survival curves overlapped. Failure to find an ad-

vantage similar to that in the Nebraska series may be due to patient numbers and disease characteristics, such as fewer good-risk patients in the Princess Margaret series. For example, 31% of their patients had bulky disease at ASCT, in contrast to 12% in the Nebraska series. In addition, 36% of their FLCL patients had bone marrow involvement, in contrast to 24% in the Nebraska series. A series of 92 follicular lymphoma patients from Stanford University included 14 with FLCL [26]. They reported results similar to those of the Nebraska group. Four-year OS and DFS were 58% and 49%, respectively. The number of FLCL patients was too small to allow for analysis of prognostic factors. However, the plateau in the survival curve for this group supports the theory that in contrast to indolent follicular lymphomas, late relapses after ASCT are uncommon.

Our study confirmed the Princess Margaret observation that follicularity does not influence outcome after ASCT for large cell lymphoma. OS was not significantly different between the FLCL and DLCL patients. Characteristics such as disease status at ASCT, chemosensitivity, and age at ASCT were the major factors predictive of OS/DFS. Other significant factors included the IPI score, the presence or absence of bulky disease, and the type of conditioning regimen. Follicular histology was not a statistically significant variable in predicting outcome. The characteristic cytogenetic abnormality of the 14,18 translocation was seen in only a minority of patients. This number was not large enough to analyze the effect on DFS. In comparison with the Princess Margaret series, we had fewer patients with bulky disease in the FLCL subgroup (19%) and also fewer with bone marrow involvement (19%). Nonetheless, we still failed to find an advantage for FLCL histology. In addition, the plateau in the survival curve supports the notion that the natural history of FLCL is similar to that of DLCL.

Our study and those of the Nebraska and Canadian series reflect the limitations of the current classification systems for follicular lymphomas. We already know from DNA microarray studies that the IPI score alone is not sufficient to reflect the differences in behavior of DLCL [27-29]. The same likely holds true for FLCL [29]. Hence, some of the observed differences in these retrospective studies likely reflect the heterogeneity of these large cell lymphomas beyond classically defined prognostic factors in ways that we cannot yet predict. We also recognize that this was a heterogenous population as a result of the retrospective nature of the study. However, when we analyzed patients by disease status, we still did not see a difference in OS or DFS between FLCL and DLCL. Thus, follicularity does not seem to predict outcome after ASCT for large cell lymphoma.

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